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## Morphological aspects of recurrent prostate cancer

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# Chapter 1



**Introduction, aim and outline of the thesis.**

## GENERAL INTRODUCTION

Prostate cancer is a considerable health risk for men throughout the world. It is a leading cause of mortality and morbidity worldwide. Adenocarcinomas make up the vast majority of prostate carcinomas. A total of 70% of prostate adenocarcinomas occur in the peripheral zone, 20% in the transitional zone, and approximately 10% in the central zone.

Transitional zone cancers show much less capsule penetration and seminal vesicle invasion than peripheral zone cancers of comparable volume because the transitional zone boundary provides a barrier to cancer spread through the peripheral zone. In peripheral zone carcinomas, capsule penetration depends largely on facilitated spread along perineural spaces, and its distribution is determined by the location of superior and inferior nerve pedicles. Capsule penetration, seminal vesicle invasion, and positive surgical margins are strongly correlated with cancer volume [1].

Other tumor types are relatively rare and include ductal adenocarcinoma, which occurs in the major ducts and often projects into the urethra; and mucinous adenocarcinoma, which secretes abundant mucin and does not arise from the major ducts. Transitional carcinoma of the prostate occurs within the ducts and, to a lesser extent, in the prostatic acini. Typically, primary transitional carcinomas are aggressive cancers that have a poor prognosis compared to the adenocarcinoma. Similarly, neuroendocrine (small-cell) tumors are rare and aggressive, have a poor prognosis, and typically require aggressive (surgical) management [2].

Accurate prostate cancer staging is mandatory in order to choose a rational treatment strategy and to determine the prognosis of the disease. The most common staging scheme is known as the TNM system, which evaluates the size of the tumor, the extent of involved lymph nodes, and any metastasis (distant spread) and also takes into account cancer grade (Table 1).

The main diagnostic tools for detecting prostate cancer include digital rectal examination (DRE), prostate-specific antigen (PSA) test and histopathological examination of prostate biopsies. DRE is the easiest and safest method of diagnosis and local staging (T stage) of prostate cancer. Because of a low information content and the subjective nature of the data, the quality of interpretation of the DRE depends largely on the experience of the physician conducting the study [3]. Still the DRE is a routine test in the clinical detection of prostate cancer and in the clinical staging process. Determination of the serum PSA concentration remains the most sensitive method for prostate cancer screening in asymptomatic men [4]. PSA is organ-specific but not cancer-specific. Thus, serum levels may be elevated in the presence of benign prostatic hyperplasia, prostatitis and other non-malignant conditions. An optimal PSA threshold value for detecting non-palpable, but

clinically significant prostate cancer is not determined, but high PSA serum levels are a strong indicator of stage and prognosis [5].

The Gleason sum score is the most common used grading system [6]. The Gleason grading consists of 5 patterns and are used in a scale from 1 to 5. The Gleason sum is one of the two most common patterns of tumour growth. For clinical grading the patterns 1 and 2 are not of importance, as they are not found in tumour bearing areas. The clinical Gleason sum score in tumour biopsies and prostatectomy specimens ranges between 6 and 10, with 6 being the least aggressive and 10 the most aggressive.

Lymph node status (clinical N-staging) needs only to be assessed when potentially curative treatment is planned. Nodal involvement is generally detected using a lymph node dissection. Conventional imaging techniques like computed tomography (CT) or magnetic resonance imaging (MRI) are usually able to detect lymph node metastases only when nodal enlargement exists, which does not occur until late in the disease process. Bone scan is indicated in patients with symptoms evocative of bone metastases.

Considering the stage of the disease different treatment options could be used. The first choice for patients with organ confined, low volume and low grade (Gleason sum 6) disease which is recognized as insignificant cancer is active surveillance [8,9]. Radical prostatectomy (RP), external beam radiotherapy (EBRT) or high dose brachytherapy are the recommended standard treatments for patients with intermediate risk, localized prostate cancer: cT2b-T2c or Gleason score = 7 or PSA - 10-20 ng/ml. There is no consensus regarding the optimal treatment of men with high (cT3a or Gleason score 8-10 or PSA >20 ng/ml) and very-high risk (cT3b-T4 N0 or any T, N1) prostate cancer. External beam radiotherapy or RP in selected cases are being recommended as options in the European Guidelines [10]. In cases of non-organ confined (T3) disease external beam radiotherapy in combination with adjuvant androgen deprivation therapy is the standard. For patients with metastatic disease androgen deprivation therapy is the first line treatment. In metastatic castration-resistant prostate cancer (CRPC), chemotherapy with docetaxel significantly improves survival [11]. Recently new hormonal treatments have been proven effective using CYP-17 inhibition [12,13] and Androgen receptor signaling inhibition [14] in pre- and post docetaxel CRPC patients. In addition, radionuclides and medical treatment for symptoms and pain relief can be used as palliative care.

Table 1. Staging of prostate cancer [7]:

<b>T Primary Tumour</b>	
<b>TX</b>	Primary tumour cannot be assessed
<b>T0</b>	No evidence of primary tumour
<b>T1</b>	Clinically inapparent tumour not palpable or visible by imaging
<b>T1a</b>	Tumour incidental histological finding in 5% or less of tissue resected
<b>T1b</b>	Tumour incidental histological finding in more than 5% of tissue resected
<b>T1c</b>	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level)
<b>T2</b>	Tumour confined within the prostate
<b>T2a</b>	Tumour involves one half of one lobe or less
<b>T2b</b>	Tumour involves more than half of one lobe, but not both lobes
<b>T2c</b>	Tumour involves both lobes
<b>T3</b>	Tumour extends through the prostatic capsule
<b>T3a</b>	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
<b>T3b</b>	Tumour invades seminal vesicle(s)
<b>T4</b>	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
<b>N Regional lymph nodes</b>	
<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Regional lymph node metastasis
<b>M Distant metastasis</b>	
<b>MX</b>	Distant metastasis cannot be assessed
<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis
<b>M1a</b>	Non-regional lymph node(s)
<b>M1b</b>	Bone(s)

## RECURRENT PROSTATE CANCER

A rise in PSA or biochemical recurrence (BCR) is the first sign of recurrent prostate cancer after curative treatment. Many patients diagnosed with localized prostate cancer are treated with RP or EBRT. Of the patients treated with RP, 15% to 46% experience recurrence of disease as detected by a rise in PSA, which is usually the first sign of recurrent prostate cancer after curative treatment [15]. Also several studies reported that 30-50% of

men treated with radiation therapy for localized prostate cancer had an increasing PSA level at a mean follow-up of 5 years [16,17].

After RP BCR is defined as a consecutive rise above a nadir of 0.2ng/mL [18]. The American Society for Therapeutic Radiology and Oncology (ASTRO) definition, Phoenix definition and a serum PSA level of  $\geq 0.5$  or  $\geq 1.0$  ng/mL are the methods used to define biochemical recurrence after radiotherapy. Currently the ASTRO-Phoenix definition is used which is defined by the nadir PSA + 2 ng/mL [19].

## **DETECTION, DIAGNOSIS AND THERAPY**

Although PSA is the most sensitive tool for detection of the recurrence, it cannot distinguish between locoregional recurrences and the presence of distant metastases after treatment [20]. PSA kinetics might be used to predict the outcome in both localized and advanced prostate cancer. However, the best way of using PSA kinetics still has to be identified.

Because DRE has a very low accuracy a transrectal ultrasound (TRUS) is often employed but also lacks sensitivity and specificity in detection of recurrent tumors.

Computed tomography (CT) and magnetic resonance imaging (MRI) are not sensitive in the detection of a local recurrence but can be used for the detection of lymph node metastases with a sensitivity of 30-80% [21,22].

At this time, there is not an imaging modality that can determine the exact localization of small volume prostate cancer. Studies are ongoing to identify novel diagnostic techniques to image prostate cancer. Molecular imaging is the main area of research on this aspect.

Possible imaging technologies are functional MRI techniques (diffusion-weighted MRI (DWI), MR spectroscopy (MRS), dynamic contrast-enhanced MRI (DCE-MRI)) and positron emission tomography (PET) [23].

PET has already been identified as promising imaging technique for detecting prostate cancer recurrence after EBRT [20,24-27]. Carbon-11-choline is one of the most commonly applied PET tracers for prostate cancer imaging [28].

Choline is a component of the phosphatidylcholines, a class of phospholipids and a major component of biologic membranes. Malignant tumors show high proliferation and increased metabolism of cell membrane components and, accordingly, an increased uptake of choline. Prostate cancer is associated with upregulated choline kinase activity and increased choline uptake. Choline can be labeled with either  $^{11}\text{C}$  ( $^{11}\text{C}$ -choline) or  $^{18}\text{F}$  ( $^{18}\text{F}$ -fluorocholine, or FCH).

Both conventional CT and PET, however, cannot detect prostate cancer foci  $< 5$  mm within the prostate.

The development of combined PET/CT cameras already has had great impact in clinical routine. In these machines a PET-camera and a CT-camera are combined to one functional unit. Thus during 1 scan session both anatomical and metabolic information are obtained. Also the resolution is increased to about 3-4 mm.

A variety of PET tracers are being investigated for targeting specific antigens/receptors, such as gastrin releasing peptide receptor (GRPR), prostate-specific membrane antigen (PSMA), prostate stem cell antigen (PSCA), among others.

With a growing interest in focal treatment of recurrent prostate cancer by ablative treatments like high intensity focused ultrasound (HIFU) and cryoablation, patient selection could be improved if the site of recurrence and its extent could be visualized.

Focal therapy can involve the local application of therapy to a specific area, and if done under real-time imaging, it then becomes 'image-guided focal therapy'.

## **AIM OF THIS THESIS**

The aim of this thesis was to study the clinical value of PET/CT in recurrent prostate cancer and explore its potential for image-guided cryoablation in future.

The following questions were addressed:

1. Does CT or PET/CT contribute to detection of small focal prostate cancer?
2. Can carbon-11-choline PET/CT identify locally recurrent prostate cancer after EBRT?
3. Is carbon-11-choline PET/CT a useful tool to predict treatment response after salvage radiotherapy?
4. Are PSA kinetics able to improve the detection rates of carbon-11-choline PET in recurrent prostate cancer after radiotherapy failure?
5. Is carbon-11-choline PET/CT a useful technique to improve selection of patients for salvage cryoablation in recurrent prostate cancer after radiotherapy failure?
6. To what extent is expression of GRPR, PSMA, VEGF and EpCAM present in recurrent prostate cancer as potential receptor for targeted imaging?

## **OUTLINE OF THIS THESIS**

**Chapter 2** reviewed the recent data on new imaging techniques which could improve the localization of small focal prostate tumors.

In **Chapter 3** we investigated the potential role of  $^{11}\text{C}$ -choline PET for the intraprostatic tumor characterization and localization in recurrent prostate cancer after EBRT.

In **Chapter 4** we evaluated the effect of total PSA and PSA kinetics on the detection rates of  $^{11}\text{C}$ -choline PET in recurrent prostate cancer after radical prostatectomy or external beam radiotherapy.

The correlation between  $^{11}\text{C}$ -choline PET/CT, time to treatment and disease specific and overall survival in biochemically recurrent prostate cancer after radical prostatectomy reported in **Chapter 5**.

In **Chapter 6** we analyzed the clinical impact of  $^{11}\text{C}$ -choline-PET/CT in the selection of patients with biochemical recurrence after radiotherapy for salvage cryoablation of the prostate.

The expression of prostate-specific membrane antigen (PSMA), epithelial cell adhesion molecule (EpCAM), vascular endothelial growth factor (VEGF) and gastrin-releasing peptide receptor (GRPR) in locally recurrent prostate cancer after brachytherapy or external beam radiotherapy (EBRT) was investigated and their adequacy for targeted imaging was analyzed in **Chapter 7**.

An English summary of the results of the studies, described in this thesis is given in **Chapter 8**. A summary in Dutch and in Russian are provided in **Chapters 9 and 10**.

In **Chapter 11** the conclusions from this thesis are given with future perspectives.



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